RESPONSE UNDER 37 C.F.R. §1.116
EXPEDITED PROCEDURE
GROUP ART UNIT 1655

Dkt. 56376/JPW/ADM

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Douglas A. Craig

Serial No.: 09/450,880 Group Art Unit: 1655

Filed : November 29, 1999 Examiner: Frank W. Lu

For : Use of Compounds Which Activate A 5-HT Receptor To Treat Urinary Incontinence

5/1/02

1185 Avenue of the Americas
New York, New York 10036
April 22, 2002

Please do not enter

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT IN RESPONSE TO DECEMBER 21, 2001 FINAL OFFICE ACTION AND PETITION FOR A ONE MONTH EXTENSION OF TIME

This Amendment is submitted in response to the Final Office Action issued December 21, 2001 by the U.S. Patent and Trademark Office in connection with the above-identified application. A response to the December 21, 2001 Final Office Action was due March 21, 2002. Applicant herewith petitions for a one month extension of time in which to respond to the December 21, 2001 Final Office Action. The fee for a one month extension of time is ONE HUNDRED TEN DOLLARS ($110.00) and a check in this amount is enclosed. With a one month extension of time, a response to the December 21, 2001 Final Office Action is due April 21, 2002. However, since April 21, 2002 is a Sunday, under 37 C.F.R. §1.7, a response may be filed on the next day which is not a Saturday, Sunday, or Federal Holiday, i.e., today, April 22, 2002. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows:

In the Claims:

Please amend claim 1 as follows:

--1. (Twice Amended) A method of treating urinary incontinence in a human subject which comprises administering to a human subject suffering from urinary incontinence a therapeutically effective amount of a 5-HT_{1F} receptor agonist which selectively activates the human 5-HT_{1F} receptor at least ten-fold more than it activates each of the human 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, and 5-HT_7 receptors.--

B1

A marked-up version of amended claim 1 showing the changes made is attached hereto as **Exhibit A.**

REMARKS

Claims 1-24 were pending in the subject application. By this Amendment, applicant has amended claim 1. Accordingly, upon entry of this Amendment, claims 1-24 as amended will be pending and under examination.

Applicant maintains that the amendments to claim 1 do not raise any issue of new matter and that this claim is fully supported by the specification as filed. Support for the amendments to claim 1 may be found inter alia in the specification as originally-filed on page 14, lines 36-37; and page 8, line 36 through page 9, line 1.

Accordingly, applicant respectfully requests that the Amendment be entered.

Rejection Under 35 U.S.C. §112, first paragraph

On page 3 of the December 21, 2001 Final Office Action, the Examiner rejected claims 1-24 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner alleged that the specification, while being enabling for treating murine incontinence with compound 1 or compound 2 which activates the human 5-HT_{1F} receptor in an *in vitro* experiment, does not reasonably provide enablement for: (1) treating any kind of subject suffering from urinary incontinence by administering a therapeutically effective amount of a 5-HT_{1F} receptor agonist which activates the human 5-HT_{1F} receptor; (2) treating any kind of subject suffering from urinary incontinence by administering a therapeutically effective amount of a 5-HT_{1F} receptor agonist which activates the human 5-HT_{1F} receptor and can treat one subject suffering from urinary incontinence; and (3) binding of any kind of 5-HT_{1F} receptor agonist that can treat one subject suffering from urinary incontinence to all receptors as recited in claims 1-24 so that all these receptors can be activated.

The Examiner concluded that the specification only shows that in an *in vitro* experiment, murine urinary incontinence can be treated with compound 1 or compound 2 and that undue experimentation is required to make the invention as it is claimed.

In response, in an attempt to advance the prosecution of the subject application, but without conceding the correctness of the

Examiner's position, applicant has amended claim 1 to recite "a human subject..." and that the 5-HT_{1F} receptor agonist "selectively activates the human 5-HT_{1F} receptor...". Claims 2-24 depend on claim 1.

Applicant maintains that the specification provides sufficient guidance and reasonably provides enablement for: (1) a human subject suffering from urinary incontinence can be treated by administering a therapeutically effective amount of a 5-HT_{1F} receptor agonist which activates the human 5-HT_{1F} receptor; (2) a 5-HT_{1F} receptor agonist that inhibits the micturition reflex in the rat DIRC model can also be effective in a human subject suffering from urinary incontinence; and (3) a 5-HT_{1F} receptor agonist that can treat one subject suffering from urinary incontinence can selectively activate a 5-HT_{1F} receptor and does not significantly activate other receptors as recited in claims 1-24.

The Examiner stated that the specification only shows that in an *in vitro* experiment, murine urinary incontinence can be treated with compound 1 or compound 2 and that undue experimentation would be required to carry out the claimed invention. Contrary to the Examiner's statement, applicant points out that Compound 1 and Compound 2 inhibit the distension-induced rhythmic contractions of the rat bladder (the DIRC model) which is an *in vivo* (not *in vitro*) model of the micturition reflex in the rat (not the mouse). See the specification on page 22, line 25 through page 23, line 37. Applicant maintains that compounds which have an inhibitory effect in the rat DIRC model are well known in the art to be predictive for treating human urinary incontinence. See the specification on page 13, lines 2-6; and page 4, line 38 through page 5, line 6.

In support of this statement, applicant encloses herewith as **Exhibit B** a Declaration Of Carlos Forray Pursuant To 37 C.F.R. §1.132 ("THE FORRAY DECLARATION"). Applicant submits this Declaration as evidence that claims 1-24 directed to methods of treating urinary incontinence in a human subject which comprise administering a 5-HT_{1F} receptor agonist which selectively activates the human 5-HT_{1F} receptor, are fully enabled by the disclosure of the subject application and that one skilled in the art would readily be able without undue experimentation to carry out the claimed methods.

Dr. Forray notes in paragraph 4 of his Declaration that in the subject application the effects of 5-HT_{1F} selective compounds on the micturition reflex were assessed by their ability to inhibit the distension-induced rhythmic contractions of the rat bladder (the DIRC model), as disclosed in the specification on page 22, line 25 through page 24, line 8. Dr. Forray then states that the DIRC model is a rat *in vivo* model that is widely considered by those skilled in the art to be predictive for the activity compounds will have in treating human urinary incontinence.

In support of his statements in paragraph 4 of his Declaration, Dr. Forray states in paragraph 5 of his Declaration that Pietra et al. (Effects of some antidepressants on the volume-induced reflex contractions of the rat urinary bladder: lack of correlation with muscarinic receptors affinity (1990) *Pharmacological Research*, 22(4): 421-432, a copy of which is attached to the Forray Declaration as Exhibit 2) teaches that the micturition reflex pathway is the same for both animals and humans and that the micturition reflex can be monitored *in vivo* by measuring the volume-induced contractions of the rat bladder. Dr. Forray notes that Pietra et al. state on page 422, lines 2-6 that "[i]n both animals and humans micturition is initiated and

maintained through the activation of a supraspinal vesicovesical micturition reflex pathway which can be monitored indirectly by recording the rhythmic, large amplitude intravesical pressure waves which occur when the bladder is distended and maintained under constant volume conditions". As noted by Dr. Forray in paragraph 4 of his Declaration, the DIRC model is also referred to as the volume-induced contractions of rat urinary bladder model.

In paragraph 6 of his Declaration, Dr. Forray states that it was well known to those skilled in the art prior to November 29, 1999 that compounds could be tested in the DIRC model to predict the activity compounds will have in treating human urinary incontinence. Dr. Forray states that one example, PCT International Publication No. WO 97/31637 (Use of 5-HT_{1A} Antagonists for the Treatment of Urinary Incontinence, published September 4, 1997, a copy of which is attached as Exhibit 3 of the Forray Declaration), teaches that 5-HT_{1A} antagonists were tested in the rat volume-induced contractions model to determine the predictive efficacy of 5-HT_{1A} antagonists for the treatment of urinary incontinence. Dr. Forray notes that PCT International Publication No. WO 97/31637 states on page 7, lines 3-5 that the described rat *in vivo* models "were originally used to validate the predictive qualities of the true serotoninergic 5-HT_{1A} receptor antagonists for the foregoing urinary tract disorders."

In paragraph 7 of his Declaration, Dr. Forray states that examples of drugs that are active in this model and are also used therapeutically in humans to treat urinary incontinence were well-known to those of ordinary skill in the art as of November 29, 1999. One example, Morikawa, K., et al. (Inhibitory effect of inaperisone hydrochloride (inaperisone), a new centrally acting muscle relaxant, on the micturition reflex (1992) *European*

Journal of Pharmacology, 213: 409-415, a copy of which is attached as Exhibit 4 of the Forray Declaration), teaches that baclofen, a compound known to be "clinically useful for the treatment of patients with unstable bladder symptoms", and oxybutynin, a compound known to be "clinically useful for the treatment of detrusor instability", are active in the DIRC model. (See Morikawa et al. on page 409, column 1, paragraph 1, lines 6-7; and page 409, column 2, lines 15-16.). Dr. Forray notes in paragraph 4 that urinary incontinence is sometimes referred to as detrusor instability or unstable bladder.

In paragraph 8 of his Declaration, Dr. Forray states that a second example, Guarneri, L. et al. (Effects of drugs used in the therapy of detrusor hyperactivity on the volume-induced contractions of the rat urinary bladder (1993) *Pharmacological Research*, 27(2): 173-187, a copy of which is attached as Exhibit 5 of the Forray Declaration), teaches that nifedipine and terodiline, "drugs most commonly utilized in the therapy of overactive detrusor", are active in the DIRC model. (See Guarneri et al. page 173, paragraph 1 of the summary, lines 1-2.). In paragraph 4, Dr. Forray notes that overactive detrusor is a condition that results in incontinence.

In paragraph 9 of his Declaration, Dr. Forray states that a third example, Pietra et al. (Exhibit 2 of the Forray Declaration) teaches that imipramine and nortryptyline are active in the DIRC model. Dr. Forray notes that Pietra et al. state on page 422, lines 7-8, that "[t]ricyclic antidepressants, particularly imipramine, have come to be accepted for the treatment of enuresis and a number of other micturition disorders." Dr. Forray notes that enuresis is incontinence (involuntary passage of urine) that occurs at night or during sleep.

In paragraph 10 of his Declaration, Dr. Forray states that those skilled in the art would also know from the teachings mentioned hereinabove that the DIRC model is useful for predicting the efficacy of compounds that have diverse modes of action. Dr. Forray states that the prior art teaches that the DIRC model is predictive for 5-HT_{1A} antagonists (see Exhibit 3), $GABA_B$ receptor agonists or anticholinergic compounds (see Exhibit 4), "mixed" anticholinergic and calcium antagonist compounds (see Exhibit 5), and tricyclic antidepressants (reuptake inhibitors) (see Exhibit 2). Dr. Forray states that these teachings support the DIRC model's wide range of applicability.

In light of Dr. Forray's Declaration, applicant maintains that the DIRC model is predictive for the activity compounds will have in treating human urinary incontinence. Applicant further maintains that the predictivity of the DIRC model is applicable to a wide range of compounds irrespective of their mode of action.

In addition, applicant maintains that the specification is enabling for a 5-HT_{1F} agonist that selectively activates the 5-HT_{1F} receptor as recited in claims 1-24. Contrary to the Examiner's point 3 above, applicant maintains that the specification does not attempt to enable a 5-HT_{1F} receptor agonist to treat urinary incontinence wherein the agonist binds to *all* the receptors recited in claims 1-24 so that *all* these receptors can be activated. For example, as indicated in Table 1 on page 25 of the specification, Compound 1 binds to the human 5-HT_{1F} receptor with a Ki affinity of 7.11 ± 0.76 nM. Compound 1 binds to the 5-HT_{1A} receptor with a Ki affinity of 367 ± 42 nM. Therefore, Compound 1 binds to the 5-HT_{1F} receptor with an affinity which is more than 50-fold greater than the affinity with which it binds to the 5-HT_{1A} receptor.

Applicant maintains that the instant specification is enabling for a method to treat a human subject suffering from urinary incontinence by administering a therapeutically effective amount of a 5-HT_{1F} receptor agonist which selectively activates the human 5-HT_{1F} receptor. The instant specification provides guidance on administering a therapeutically effective amount of a 5-HT_{1F} receptor agonist to a human subject on page 13, line 8 through page 15, line 2. Applicant maintains that the described *in vivo* model correlates with drug efficacy in humans for the treatment of urinary incontinence. Applicant further maintains that the claims are enabled for selectively activating the 5-HT_{1F} receptor.

Applicant further maintains that no undue experimentation is required for the skilled artisan to practice the claimed invention.

Accordingly, in view of the remarks and amendments made hereinabove, applicant respectfully requests that the Examiner reconsider and withdraw the ground of rejection set forth in the December 21, 2001 Final Office Action and earnestly solicits allowance of the claims now pending in the subject application, namely claims 1-24.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $110.00 fee for a one month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if an additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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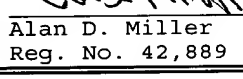
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



Alan D. Miller Date
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